Specialty Conference

Common Causes of Cardiac Emboli—Left Ventricular Thrombi and Atrial Fibrillation

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

JOHN R. STRATTON, MD*: Emboli from cardiac sources can lodge in the brain or the periphery. Embolism to the periphery, such as to the kidneys, spleen, or extremities, is frequently clinically silent, but embolism to the brain is usually symptomatic. Therefore, the distribution of clinically detected emboli is roughly three-quarters cerebral and one-quarter peripheral. Cardiac emboli are a relatively common cause of stroke syndromes, accounting for about 13% of all strokes, with about two thirds of these embolic events leading to serious morbidity or death.[1,2]

The sources of cardiogenic emboli are listed in Table 1. Rheumatic mitral valve disease was previously the leading source of cardiogenic embolism but is now an infrequent cause. Currently about 45% of all cardiogenic emboli are associated with nonvalvular atrial fibrillation, and 25% are associated with acute or chronic myocardial infarction.[1] Most emboli in patients with atrial fibrillation are due to left atrial thrombi, and most emboli in patients with ischemic heart disease arise from left ventricular thrombi. The remaining 20% of cardiac emboli are due to prosthetic heart valves, nonbacterial thrombotic endocarditis, bacterial endocarditis, mitral prolapse, tumors, idiopathic cardiomyopathy, and other rarer disorders.

There has been a recent proliferation of useful information concerning the two leading causes of cardiogenic emboli, atrial fibrillation and left ventricular thrombus. Left ventricular thrombus has been recognized as a clinically important disorder only in the current decade, with the development of imaging modalities capable of detecting a thrombus during life. In addition, the importance of nonvalvular atrial fibrillation as a cause of stroke has only recently been appreciated. In the rest of this discussion I will focus on these two common causes of cardiogenic emboli and will review the recommended anticoagulant therapy after an embolic event has occurred.

Left Ventricular Thrombi

Diagnosis of Left Ventricular Thrombi

Until recently, the accurate diagnosis of a left ventricular thrombus was possible only at the time of autopsy. Left ventricular thrombus was suggested clinically if a systemic embolus occurred but, even when suspected, could not be proved during life.

Several imaging techniques are capable of detecting left ventricular thrombi (Table 2). With the exception of radionuclide imaging using platelets labeled with indium 111, all of the listed techniques detect a space-occupying lesion within the left ventricle. Both invasive contrast angiography[3-5] as done at the time of cardiac catheterization and radionuclide angiography[4-6] detect thrombi as areas of negative or absent contrast; the sensitivity of these two techniques is low, in the range of 31% to 62%. X-ray computed tomographic (CT) scanning[7,8] and magnetic resonance imaging[9] are both capable of generating images of left ventricular thrombi, but the diagnostic accuracy of these techniques has not been defined. Furthermore, these techniques are expensive and not widely available.

Indium 111 platelet imaging provides information about left ventricular thrombi that is not available with other techniques.[10,14,15] With this technique, autologous platelets are labeled and reinjected into the patient. Serial imaging is then carried out over a period of four to five days (Figure 1). The half-life of the isotope is three days, which allows repeat imaging for as long as a week. Left ventricular (LV) thrombi are detected as localized areas of uptake in the left ventricle. Because this technique can estimate thrombus activity, it provides unique information about LV thrombi. For example, ^{111}In-platelet imaging has shown that most thrombi have continuing platelet uptake regardless of the age of the thrombus.[10,14,15] Thrombi that have been excised at the time of an operation following platelet labeling have radioactivity ratios of approximately 10:1 to 355:1 compared with whole blood, indicating active platelet deposition on the thrombus surface.[10,11] The sensitivity of platelet imaging for detecting LV thrombi is 71%, and the specificity is 100%.[11]

In contrast to the information about thrombus activity obtained by platelet imaging, echocardiography gives information about the anatomic location, size, and morphologic features of thrombi. A study done at the University of Washington found a sensitivity of 86% and a specificity of 95%,[11] and subsequent studies have confirmed these findings.[4,5,12,13]

Echocardiography, however, does have several limita-

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
INR = international normalized ratio
LV = left ventricular

tions for the diagnosis of left ventricular thrombus. About 5% to 10% of studies are technically poor and cannot adequately exclude the presence of a thrombus. Anatomic structures such as trabeculations, aberrant bands, papillary muscles, and tumors are occasionally mistaken for LV thrombi and cause falsely abnormal ("false-positive") studies.[11,16,17] In addition, echocardiographic artifacts due to noise or resolution problems cause false-positive studies.[11,18] Nevertheless, because of its wide availability, relative inexpensiveness, and lack of radiation exposure, echocardiography is the method of choice for diagnosing left ventricular thrombus. When technically inadequate studies occur or concern exists about a potentially false-positive study, other more expensive diagnostic techniques such as platelet imaging or contrast-enhanced x-ray CT are alternatives.

Left Ventricular Thrombi in Acute Myocardial Infarction

Prevalence and time of formation. Substantial evidence indicates that LV thrombi occur almost exclusively in association with anterior myocardial infarctions (Table 3). They develop in about a third of patients who have anterior transmural myocardial infarctions. In contrast, their occurrence in patients with inferior transmural infarctions or with non-Q wave infarction is rare.[19-24] The predominant development of left ventricular thrombi in anterior wall infarctions in contrast to other types of infarction is partially explained by several factors. Apical akinesis, or dyskinesis, appears to be a nearly uniform prerequisite for the development of a thrombus, and apical wall motion abnormalities are much more common with anterior infarctions than with other infarctions. In addition, anterior infarctions are larger than inferior infarctions, which predispose both to a stasis of blood and to an increased release of substances that promote local thrombus formation. Anterior infarctions are also more commonly associated with aneurysm formation with resultant blood stasis than are other types of infarctions. One study has suggested that left ventricular thrombus formation is increased in patients with transmural anterior infarctions treated with the β-blocker timolol maleate, possibly because of greater apical wall motion abnormalities.[25]

The time of left ventricular thrombus formation following infarction has been described in several studies in which serial echocardiograms were done.[20-22,24,33,34] Few thrombi (0% to 14%) are present within 24 hours of the onset of infarction. Within 48 hours of infarction, only 46% to 55% of thrombi are present, but within a week of infarction, nearly all thrombi (83% to 100%) have formed. In one study,

TABLE 1.—*Cardiac Sources of Embolic Stroke*

Cardiac Disease	*Approximate Percentage of All Embolic Strokes, %*
Ischemic heart disease—acute or chronic infarction	25
Nonvalvular atrial fibrillation	45
Valvular heart disease	10
Prosthetic heart valves	10
Other—prolapse, endocarditis, tumors, paradoxic emboli, cardiomyopathy	10
	100

TABLE 2.—*Diagnostic Techniques for Detecting Left Ventricular Thrombi*

Diagnostic Technique	*Sensitivity, %*	*Specificity, %*
Two-dimensional echocardiography*	77-95	88-100
Indium 111 platelet imaging†	71	100
Radionuclide angiography‡	31-62	92-100
Contrast angiography§	31-62	75-100
X-ray computed tomography‖	....	....
Magnetic resonance imaging¶	....	....

*From Pechacek et al,[4] Starling et al,[5] Ezekowitz et al,[10] Stratton et al,[11] Visser et al,[12] and Lupi et al.[13]
†From Stratton et al,[13] Stratton et al,[14] and Bellotti et al.[15]
‡From Pechacek et al,[4] Starling et al,[5] and Stratton et al.[6]
§From Reeder et al,[3] Pechacek et al,[4] and Starling et al.[5]
‖From Tomoda et al[7] and Nair et al.[8]
¶From Higgins et al.[9]

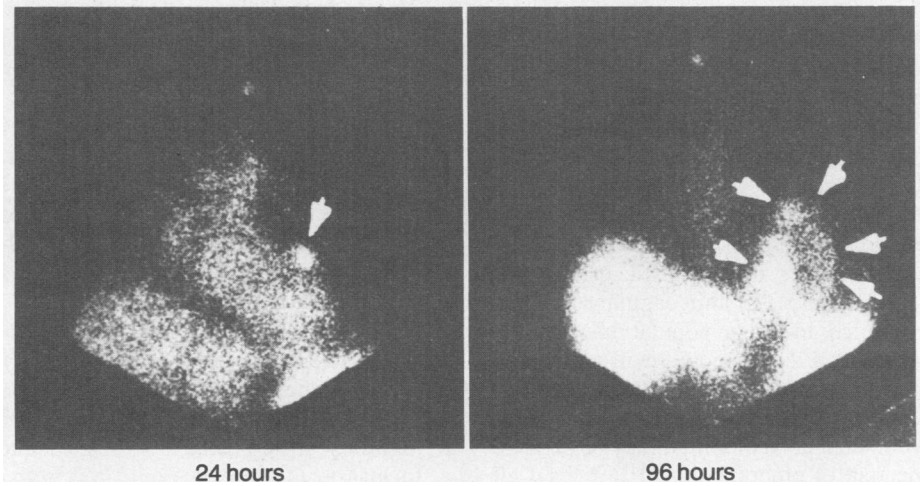

Figure 1.—Anterior views of imaging using platelets labeled with indium 111—300,000 counts per view—were taken at 24 and 96 hours following the ^{111}In-platelet injection. The localized platelet uptake **(arrows)** denotes a left ventricular thrombus. The images are more pronounced at 96 hours than at 24 hours owing to the continued accretion of labeled platelets onto the thrombus and to a reduction in circulating background blood pool activity. The liver is at the lower left and the spleen at the lower right of both images.

TABLE 3.—*Risk of Systemic Embolization If Left Ventricular Thrombus Present in Acute Myocardial Infarction*

Source	Patients With Thrombi, No.	Patients Receiving Anti-coagulants,* No.	Mean Follow-up, mo	Emboli Before or After Echo†
Asinger et al, 1981[20]	12	7	7	0/12 (0)
Friedman et al, 1982[26]	11	9	11	2/11 (18)
Keating et al, 1983[27]	17	10	8	6/17 (35)
Haugland et al, 1984[28]	31	NA	10	9/31 (29)
Johannessen et al, 1985[23]	15	15	0.5	4/15 (27)
Visser et al, 1984[22]	22	22	12	1/22 (4)
Weinreich et al, 1984[19]	43	18	10	7/43 (16)
Spirito et al, 1985[21]	24	0	7	1/24 (4)
Visser et al, 1985[29]	46	NA	NA	12/46 (26)
Tramarin et al, 1986[30]	34	17	12	1/34 (3)
Domenicucci et al, 1987[24]	59	0	14	5/59 (8)
Johannessen et al, 1988[31]	55	55	3	15/55 (27)
Turpie et al, 1988[32]	33	8	0.4	3/33 (9)
Overall	402	161		66/402 (16)

echo=echocardiogram, NA=not available

*Heparin or sodium warfarin were used in anticoagulation therapy.
†The numbers represent the number of systemic embolic events versus the number of patients with left ventricular thrombi (%).

12% formed later than two weeks.[24] The mean time to thrombus formation was about 5 days in one study[20] and 12 days in another.[24] Thus, an echocardiogram done within the first several days of infarction cannot exclude the possibility of later thrombus development. Because of the relatively wide variability in the time of thrombus formation and the probable efficacy of early anticoagulation in preventing thrombus formation, it is unreasonable to adopt a treatment strategy that requires the echocardiographic diagnosis of a thrombus before instituting anticoagulant therapy.

Embolic risk of left ventricular thrombi in acute infarction. The presence of a left ventricular thrombus is associated with a considerable risk of systemic embolization. In the largest available study of 150 patients with a first anterior wall infarct, 27% of the patients in whom LV thrombi developed suffered systemic emboli within three months.[23] In contrast, only 2% of patients with anterior infarction in whom LV thrombi did not develop suffered systemic emboli. Although most large studies have shown a substantial embolic risk—and the risk pooled from all studies is about 16%—as shown in Table 3, agreement has not been uniform that LV thrombi are associated with such an increased risk. The range of reported embolic events in studies of patients with echocardiographically detected thrombi has varied between 0% and 35%.[19-24,26-32] The discrepancies are difficult to reconcile but may be due in part to retrospective versus prospective data collection, differences in diagnostic criteria for thrombus or embolus, differences in anticoagulant therapy, and other baseline differences in patient populations.

Predictors of embolization. No clinical features strongly predict embolization in a patient with a left ventricular thrombus. Two echocardiographic features, however, thrombus protrusion and thrombus mobility, may be of some use for predicting the risk of embolization.[28,29,31,35] Of all thrombi, 34% to 55% protrude into the ventricular cavity, and the rest are flat; protruding thrombi are associated with embolization in 22% to 56% of cases, but flat thrombi are associated with embolization in only 3% to 13% of cases. Thrombus mobility, defined as the movement of a thrombus independent of the underlying myocardium, occurs in 15% to 27% of thrombi, and the remainder of thrombi are immobile; between 35% and 83% of patients with a mobile thrombus suffer systemic embolization compared with only 5% to 16% of patients with immobile thrombi.

Although those features are of some use in predicting the embolic risk, spontaneous changes in these features are common in patients with acute myocardial infarction. Domenicucci and co-workers noted that 41% of patients had changes in thrombus shape and 29% had changes in thrombus mobility over a 14-month follow-up after an acute infarction.[24] In contrast, among 48 patients with chronic myocardial infarction or cardiomyopathy, we noted changes in thrombus shape in only 16% and changes in thrombus mobility in only 10% over a two-year follow-up.[36]

Among 58 patients with LV thrombi diagnosed by echocardiography, we noted a higher embolic rate in patients who also had a positive ^{111}In-platelet image (23%, 7 of 30) compared with patients with a negative platelet image (4%, 1 of 28) during a 38-month follow-up.[37] Thus, thrombosis imaging may stratify the embolic risk in patients with left ventricular thrombi diagnosed by echocardiography.

Preventing left ventricular thrombi with early anticoagulation. In two older studies of anticoagulation in patients with acute infarction, the autopsy prevalence of LV thrombi was reported in a total of 112 patients who were randomly assigned to receive either early or no anticoagulation. Among non-anticoagulated patients, 49% had a left ventricular thrombus at autopsy compared with only 19% of patients who were anticoagulated.[38,39] These data suggested that early anticoagulation in myocardial infarction reduces the prevalence of left ventricular thrombi.

Using echocardiographic detection of LV thrombi as the end point, the role of early heparin and sodium warfarin therapy in preventing left ventricular thrombi was examined in five recent randomized clinical trials (Table 4).[32-34,40,41] In all series, full-dose heparin therapy was used and serial echocardiograms were done. The trials varied in the dose of heparin and the therapy, if any, for the control group. The results from these studies, completed in Australia,[34] France,[33] Norway,[40] Canada,[32] and the United States,[41] are conflicting. The study by Davis and Ireland reported no apparent benefit, but both the anticoagulated and control groups had an unusually high prevalence of thrombus formation (56%).[34] The study by Arvan and Boscha found no benefit, but only 30 patients were included.[41] The study by Gueret and associates reported a trend toward a reduction in LV thrombi from 52% to 38% among patients receiving early heparin therapy compared with controls, but this was not statistically significant.[33] In the Norwegian trial, a thrombus developed in 21% of control patients compared with 0% of the patients treated with heparin therapy ($P < .05$).[40]

The largest study, by Turpie and colleagues, randomly assigned patients with a first anterior myocardial infarction to receive either fixed full-dose heparin, 12,500 units twice a day, or to low-dose heparin, 5,000 units twice a day; the high-dose group had a significant reduction in LV thrombus formation at ten days compared with controls (9% versus 31%, $P < .01$).[32] Many of the patients in whom LV thrombi developed despite high-dose heparin therapy had subtherapeutic heparin levels, suggesting that titrating the dose may be better than a fixed dosing schedule. Thus, the available data, although somewhat conflicting, suggest that early full-

TABLE 4.—*Randomized Trials of Full-Dose Anticoagulation to Prevent Left Ventricular (LV) Thrombi in Acute Myocardial Infarction*

Source	Patients, No.	Hours to Randomization or Treatment	Anticoagulant Regimen‡	Control Regimen	Time of Last Echo, days	LV Thrombi		
						Treated, %	Control, %	P Value
Nordrehaug et al, 1985[40]	53	4.6±2.5†	Heparin, warfarin	Placebo	10	0	21	<.05
Davis and Ireland, 1986[34]	52	<12*	Heparin, warfarin	Low-dose heparin; warfarin if creatine kinase >1,000 U/liter	7-14	56	56	NS
Gueret et al, 1986[33]	46§	5.2±4.6*	Heparin	No therapy	20-50	38	52	NS
Arvan and Boscha, 1987[41]	30	6.5±3.3†	Heparin, warfarin	No therapy	14	31	35	NS
Turpie et al, 1988[32]	167	<36*	Heparin, 12,500 b.i.d.	Heparin, 5,000 b.i.d.	10	9	31	<.01
Total	348							

b.i.d.=twice a day, echo=echocardiogram, NS=not significant

*Hours to randomization.
†Hours to treatment.
‡All studies except Turpie et al used adjusted-dose anticoagulants.
§This study included only patients with anterior wall myocardial infarctions.

TABLE 5.—*Systemic Emboli in Patients With Acute Myocardial Infarction Receiving Anticoagulation Versus Control Regimen: Data From Randomized Trials for Left Ventricular (LV) Thrombus Prevention**

Source	Follow-up Duration, mo	Systemic Embolic Events	
		Patients Receiving Full-Dose Anticoagulants	Patients on Control Regimen
Nordrehaug et al, 1985[40]	~0.5	0/26	1/27
Davis and Ireland, 1986[34]	~0.5	0/27	1/25
Gueret et al, 1986[33]	0.6-1.7	1/21	1/25
Arvan and Boscha, 1987[41]	1	1/17	1/13
Turpie et al, 1988[32]	~0.5	1/83	3/84
Overall		3/174 (1.7%)	7/174 (4.0%)

*These data refer to all treated and control patients, whether or not an LV thrombus developed.

dose anticoagulation reduces LV thrombus formation in cases of acute anterior infarction.

No studies to date have shown any benefit of platelet inhibitory agents in decreasing left ventricular thrombus formation. In one randomized trial of 100 patients with acute myocardial infarction, Funke Küpper and co-workers found no reduction in LV thrombus formation using sulfinpyrazone plus oral anticoagulants compared with using oral anticoagulants only (20% in both groups).[42] In a subsequent randomized study in 100 patients, they found that the use of aspirin, 100 mg a day, did not result in a reduction in LV thrombus formation compared with placebo (33% in both groups).[43] In a randomized trial of patients with a first anterior wall myocardial infarction, we found no reduction in LV thrombus formation in patients treated with aspirin plus dipyridamole compared with placebo-treated patients.[44] Two studies have suggested that intracoronary streptokinase does not reduce LV thrombus formation,[45,46] whereas one small nonrandomized uncontrolled trial suggested that administering intravenous streptokinase did reduce LV thrombus formation.[47]

Reduction in embolic events with early anticoagulation. In addition to the probable effectiveness of acute anticoagulation for reducing thrombus formation, substantial evidence suggests that early anticoagulation more importantly reduces the risk of stroke. In three large older randomized trials of anticoagulation in acute myocardial infarction, a total of 3,562 patients in whom the presence or absence of left ventricular thrombi was unknown were studied.[38,39,48,49] In each study, there was a reduction in systemic emboli, which was 55% for one trial ($P<.01$),[48] 24% for another (P=NS),[39] and 75% for a third ($P<.01$).[38] Approximately 2% to 6% of patients in the control groups had embolic events, compared with only 1% to 2% of patients in the anticoagulated groups. In all three trials, the bleeding risk was higher in the anticoagulated groups, as would be expected. Bleeding occurred in 5% to 13% of patients receiving anticoagulants but in only 1% to 5% of controls.[50] There were no cases of fatal bleeding in any of the trials, however. Thus, anticoagulation of all patients with an acute myocardial infarction reduces systemic emboli but exposes some patients with a low embolic risk to possible bleeding complications. Given our current knowledge that left ventricular thrombi develop in patients with anterior myocardial infarctions, therapy can be targeted to this high-risk group.

At present, there are relatively few data concerning the efficacy of early anticoagulation in reducing the risk of systemic emboli. The recent randomized trials of anticoagulation for LV thrombus prevention were too small and had too short a follow-up to definitively assess embolism as an end point. Nevertheless, when all studies were pooled, there was a trend for a reduction in embolic events from 4.0% (7 of 174) in control patients to 1.7% (3 of 174) in patients receiving anticoagulation during a brief follow-up (Table 5).[32-34,40,41]

The potential effects of anticoagulant therapy in patients in whom LV thrombi have developed are summarized in Table 6. Only studies that reported on both anticoagulated and non-anticoagulated patients are included. Overall, there is a trend for a reduction in embolic events among patients with LV thrombi treated with full-dose anticoagulation compared with untreated patients with LV thrombi (5% versus 18%).[19,20,26,27,30,32-34,41]

Recommendations for anticoagulation in acute myocardial infarction. Patients who have an anterior transmural myocardial infarction should receive full-dose heparin therapy followed by warfarin therapy for three months to prolong the prothrombin time to an international normalized ratio (INR) of 2.0 to 3.0—which corresponds to a prothrombin time of 1.2 to 1.5 times a control time using a rabbit brain thromboplastin reagent.[49,51] Therapy should be instituted as early as possible, based on a history and electrocardiogram suggestive of acute anterior infarction, because early therapy reduced thrombus development. This regimen, in addition to preventing the development of thrombi in many

TABLE 6.—*Systemic Emboli in Patients in Whom Left Ventricular Thrombi Develop in Acute Infarction: Possible Efficacy of Anticoagulant Therapy*

Source	Duration of Follow-up, mo	Systemic Embolic Events* Full-Dose Anticoagulants		No Full-Dose Anticoagulants	
Asinger et al, 1981[20]	7	0/5	(0)	0/7	(0)
Friedman et al, 1982[26]	11	1/9	(11)	1/2	(50)
Keating et al, 1983[27]	11	0/10	(0)	6/7	(86)
Weinreich et al, 1984[19]	15	0/25	(0)	7/18	(39)
Davis and Ireland, 1986[34]	<1	0/14	(0)	1/15	(7)
Gueret et al, 1986[33]	0.6-1.7	1/8	(12)	1/13	(8)
Tramarin et al, 1986[30]	12	1/17	(6)	0/17	(0)
Arvan and Boscha, 1987[41]	<1	1/4	(25)	1/6	(17)
Turpie et al, 1988[32]	<1	1/8	(12)	3/25	(12)
Overall		5/100	(5)	20/110	(18)

*The numbers represent the number of embolic events versus the number of patients in each group with left ventricular thrombi (%).

patients, enhances the resolution of formed thrombi. Most important, the risk of embolization is reduced.

In patients with inferior wall myocardial infarctions or nontransmural infarctions, low-dose heparin therapy, 5,000 units intravenously or subcutaneously every 12 hours, should be given until a patient is fully ambulatory to prevent venous thromboembolism.[49] In addition, some authors recommend that patients with inferior wall or nontransmural infarctions who are at an increased risk of systemic embolism because of atrial fibrillation, congestive heart failure, or a history of systemic or pulmonary embolus also receive the same heparin-warfarin regimen as patients with anterior transmural infarctions. The evidence of benefit in these patient groups is limited, however. All subjects should receive aspirin, 325 mg initially, and 325 mg per day subsequently unless a contraindication to using aspirin is present.[49]

These recommendations do not require the use of echocardiography but rely solely on electrocardiographic criteria. Waiting for an echocardiogram to show a left ventricular thrombus misses the opportunity to prevent thrombus formation and can lead to unnecessary echocardiograms.

Many patients, particularly those with anterior wall infarctions, now receive early thrombolytic therapy with tissue plasminogen activator or streptokinase. Because the available data suggest that thrombolytic therapy does not reduce the risk of left ventricular thrombus formation, it is probably reasonable to apply the same anticoagulant guidelines noted above to patients following thrombolytic therapy, although the use of heparin following intravenous streptokinase was associated with increased bleeding in the Second International Study of Infarct Survival.[52] Whether early angioplasty reduces the risk of left ventricular thrombus development and therefore the risk of embolization is unknown. Currently it is probably prudent to follow the same guidelines for anticoagulation noted earlier in patients with anterior wall infarctions who have early angioplasty. Additional studies are clearly needed to clarify the role of heparin and warfarin therapy, with or without platelet inhibitor therapy, in patients treated with thrombolytic agents or angioplasty.

Embolic Risk of Chronic Left Ventricular Thrombi

Much less is known about the fate and embolic potential of left ventricular thrombi that are present months to years following myocardial infarctions or in patients with idiopathic cardiomyopathy. Persistent left ventricular thrombi are common following a myocardial infarction. Approximately 24% of patients dying with a healed infarct have a left ventricular thrombus compared with 37% of patients dying with an acute infarction.[53] The recognized prevalence among living patients with remote infarction, however, is lower—about 10% to 14%. The relatively high prevalence of chronic thrombi can be attributed to the low rate of the spontaneous resolution of thrombi. In recent studies, only about a quarter of untreated patients with left ventricular thrombi had thrombus resolution over a 3- to 12-month period.[21,54] Therefore, thrombus resolution is uncommon without therapy.

Retrospective studies have suggested a substantial embolic risk—7% to 19%—due to chronic left ventricular thrombosis.[29,31,55] To define prospectively the embolic risk, 85 patients with LV thrombi predominantly due to remote myocardial infarction were observed at the University of Washington.[35] A control group was also observed because of the diagnostic uncertainty concerning the etiology of central nervous system events in a population of patients with diffuse atherosclerosis. The control group consisted of 91 patients who did not have LV thrombi but who were otherwise similar to the patients who did. The mean follow-up was 22 months, and emboli were strictly defined by criteria recently developed by Hart and associates.[56] Both groups had a low ejection fraction; the mean time from the last infarction was 32 months in the LV thrombus group and 48 months in the control group.

During follow-up, 13% of subjects with LV thrombi had embolic events compared with 2% of control subjects ($P<.01$). By life-table methods, at two years of follow-up 97% of control subjects were embolus-free compared with 86% of patients with thrombi ($P<.01$).[35] These data document that patients with LV thrombi present at times remote from an acute myocardial infarction are at an increased risk for systemic embolization.

The correct anticoagulant therapy, if any, for patients with chronic left ventricular thrombi remains unknown. The recent National Heart, Lung, and Blood Institute's National Conference on Antithrombotic Therapy offered no recommendations for the management of patients with chronic thrombi. In a small number of patients with chronic thrombi, we have shown that the use of the combination of aspirin plus dipyridamole or sulfinpyrazone alone inhibits platelet uptake, as shown by platelet imaging in some patients with chronic left ventricular thrombi. Warfarin therapy also resolved thrombi in some cases and may lead to decreased thrombus activity in other cases.[57]

In our study, warfarin therapy was at the discretion of the individual physician. Among 23 warfarin-treated patients, 2 (9%) had emboli, but both emboli occurred within the first five days of therapy; among 62 nontreated patients, 9 (14%) had emboli. Warfarin therapy, however, was associated with bleeding complications in 20% of treated patients observed for a mean of 13 months.[35]

The risks associated with long-term warfarin administration have been comparable in other much larger trials in patients with ischemic heart disease, with an overall pooled bleeding risk of 23%, a major bleeding risk of 4.7%, and a fatal bleeding risk of 1.0% in patients who were on long-term anticoagulation.[50] Because the bleeding risk of long-term full-dose anticoagulation may outweigh the risk of

embolism, the proper therapy for patients with chronic left ventricular thrombus is unclear. Two alternatives with a potentially lower risk are lower intensity warfarin therapy and platelet-inhibitory agents, but neither approach has been tested prospectively to determine if it would reduce the embolic rate. The current practice at the University of Washington is to not treat patients who have chronic thrombi with a full-dose warfarin regimen unless they have suffered a previous embolus or unless echocardiographic features (thrombus protrusion and motility) suggest a high risk of embolization.

Left Ventricular Thrombi and Left Ventricular Aneurysms

About half of all patients with chronic left ventricular aneurysms have associated left ventricular thrombi. Retrospective studies have suggested, however, that the risk of embolization in patients with left ventricular aneurysms is low despite the high prevalence of left ventricular thrombus. The prevalence of embolization found in three retrospective reviews was only 1% to 5%.[3,58,59] The studies may have been biased against including patients with emboli because participating patients had to be fit enough to undergo cardiac catheterization, surgical treatment, or both. Recent echocardiographic data from Haugland and colleagues and from the University of Washington suggest that the presence of an associated aneurysm does not reduce the risk of embolization.[28,35] In our prospective study, emboli occurred in 13% of patients with thrombi and aneurysm, compared with 14% of patients with thrombi and no aneurysm.

Atrial Fibrillation and Embolic Risk

Systemic Embolism in Rheumatic Heart Disease

Among all patients with rheumatic mitral valvular disease, the lifetime risk of systemic embolization if atrial fibrillation is present is substantially increased, with a minimum estimate being 20%.[60] The risk of systemic embolism with atrial fibrillation is at least four times that with sinus rhythm.[60,61] Overall, the embolic rate was 5.2% per year for patients who were in atrial fibrillation in one study compared with 0.7% for patients in normal sinus rhythm.[62] This increased risk exists both for patients with rheumatic mitral stenosis and for patients with mitral regurgitation.[63]

In patients with rheumatic heart disease, about 82% of all emboli occur while the patient is in atrial fibrillation.[60] The overall prevalence of emboli is 7% in patients with sinus rhythm but 30% in patients with atrial fibrillation.[61] Left atrial thrombus appears to be the source for most of these emboli, as indicated by data showing that about 41% of patients with rheumatic atrial fibrillation have associated left atrial thrombi compared with only 9% of patients in normal sinus rhythm.[60] Fully 87% of patients with atrial thrombi are in atrial fibrillation. Approximately 41% of patients with left atrial thrombi have emboli compared with 16% or less of patients without left atrial thrombi.[60]

Several studies suggest a considerable reduction in the systemic embolic rate with anticoagulation in patients with rheumatic mitral valve disease and atrial fibrillation who have already suffered an embolus.[60-65] There are no controlled trials of anticoagulation of patients who have not yet had an embolus. In an observational study by Szekely, warfarin-treated patients had an embolic rate of 4.2 per 100 patient-years compared with 6.8 in non-anticoagulated patients.[62]

Because of the established high risk of emboli in patients with rheumatic heart disease who have chronic atrial fibrillation, the current recommendation is to anticoagulate all patients in this group at a low intensity (INR of 2.0 to 3.0).[59] All patients with systemic emboli, regardless of their current rhythm, should be anticoagulated at a high intensity (INR of 3.0 to 4.5).[1,59] There is much less agreement concerning the anticoagulation of patients with rheumatic heart disease who are in normal sinus rhythm. Some groups have suggested that patients in normal sinus rhythm with severe left ventricular dysfunction, a large atrium, or a left atrial clot should receive long-term anticoagulation.

Embolization in Nonvalvular Atrial Fibrillation

Nonvalvular atrial fibrillation is a recently adopted term for an old disease. As a diagnostic category, it encompasses all patients with atrial fibrillation except those with substantial mitral stenosis or regurgitation. Nonvalvular atrial fibrillation is largely a disease of aging and develops in about 5% of people older than 65 years.[66] Other conditions associated with nonvalvular atrial fibrillation include ischemic heart disease, thyrotoxicosis, hypertension, dilated cardiomyopathy, and hypertrophic cardiomyopathy. Although at least one of these conditions will occur in most people with nonvalvular atrial fibrillation, about 10% to 15% of patients will have so-called idiopathic or "lone" atrial fibrillation without another associated disease.

Nonvalvular atrial fibrillation is important because it is a risk factor for stroke.[1,61] An early indication that nonvalvular atrial fibrillation was not a benign disorder came from an autopsy study that showed a 30% prevalence of embolization in patients with nonvalvular atrial fibrillation, which was similar to the 40% prevalence of embolization in patients with rheumatic mitral valve disease. The embolic prevalence was only 7% in control patients with normal sinus rhythm.[67]

The current knowledge about the stroke risk due to nonvalvular atrial fibrillation has been derived largely from the Framingham study in which 5,191 patients were observed.[66,68-70] Nonvalvular atrial fibrillation increased the risk of stroke fivefold.[68,69] The annual risk of stroke was about 5% per year, and the lifetime risk of stroke was about 30%. Moreover, the risk of recurrence after a first stroke with nonvalvular atrial fibrillation was high. The increased risk of stroke was independent of associated cardiac failure, coronary heart disease, and hypertension. The contribution of atrial fibrillation to the risk of stroke was at least as powerful as other common risk factors including age, systolic blood pressure, congestive heart failure, and coronary artery disease. The risk of stroke associated with nonvalvular atrial fibrillation appeared to increase with age. Only 9% of stroke patients in the 55- to 64-years age group had associated atrial fibrillation, whereas 40% of stroke patients older than 85 years had associated atrial fibrillation.

The importance of atrial fibrillation as a risk factor for stroke was noted in the subset of the Framingham population that had lone or pure atrial fibrillation unassociated with other diseases that predispose to stroke.[70] Of all patients with atrial fibrillation in the Framingham study, 11% had lone or pure atrial fibrillation; with lone atrial fibrillation, the risk of stroke was four times greater than for control patients.[70] Overall, 27% of the patients with lone atrial fibrillation had strokes.

A recent study from the Mayo Clinic, however, reported a low risk of stroke in patients with lone atrial fibrillation. Among all patients with atrial fibrillation, 97 (2.7%) were classified as having lone atrial fibrillation. The criteria for lone atrial fibrillation were age younger than 60, no hypertension, ischemic heart disease, congestive heart failure, any mitral valve disease, and no lung disease. Most of these patients had paroxysmal atrial fibrillation; only 22% had chronic atrial fibrillation. In this highly selected group, only 4 (4%) had embolic strokes over a 15-year follow-up.[71]

There is no consensus as to whether anticoagulation should be prescribed for patients with nonvalvular atrial fibrillation.[61] In practice, warfarin is rarely used because of the known bleeding risk. In addition, the relatively substantial risk of stroke has only recently been appreciated. In a recently reported trial, however, a benefit of warfarin therapy is strongly suggested. In this trial, 1,007 patients with nonrheumatic atrial fibrillation were randomly assigned to receive either high-intensity warfarin (INR of 2.8 to 4.2; $n = 335$), aspirin (75 mg daily; $n = 336$), or a placebo ($n = 336$).[72] The incidence of thromboembolic complications—stroke, transient ischemic attack, or peripheral emboli—and vascular death was reduced with warfarin therapy but not with aspirin. The yearly incidence of thromboembolic complications was 2.0% with the use of warfarin and 5.5% with aspirin and with placebo. There were more nonfatal bleeding episodes with warfarin therapy ($n = 21$) than with the use of aspirin ($n = 2$) or placebo ($n = 0$), but only one fatal bleeding episode. Several additional randomized studies, which are assessing less intense warfarin therapy, are currently underway.

Anticoagulation for Elective Cardioversion of Atrial Fibrillation

The most comprehensive data regarding the risk of embolization following elective cardioversion was reported from a nonrandomized study in Sweden.[73] Bjerkelund and Orning showed a substantially lower risk of systemic embolization following cardioversion among patients receiving anticoagulation compared with patients not receiving anticoagulation (0.8% versus 5.3%).[73] In the subset of patients with nonvalvular atrial fibrillation, the prevalence of emboli was reduced from 7.8% to 1.3%. The current recommendation is to anticoagulate patients for three weeks before elective cardioversion and for an additional four weeks after cardioversion at a low intensity (INR of 2.0 to 3.0).[61] For atrial fibrillation of a short duration—less than three days—and for patients with atrial flutter or supraventricular tachycardia, anticoagulation is not recommended.[61]

Anticoagulation Following Cerebral Embolism

There are many causes of ischemic stroke syndromes. In a given patient, it is often difficult to determine whether a stroke is caused by a cardiogenic embolus, cerebrovascular atherosclerosis, or another disorder. The clinical differentiation based on history, physical examination, and diagnostic test results has recently been outlined by Sherman and coworkers.[1,2] Of patients with a known potential cardiac source of embolization (most commonly left ventricular thrombi or atrial fibrillation), perhaps 50% to 70% of stroke syndromes that occur are due to the cardiac source and the rest are due to noncardiac disorders.

If a cardiogenic brain embolus is diagnosed, the risk of recurrent stroke within the first month following a cerebral embolic event is about 12% for patients who do not receive anticoagulation.[1] Recurrent emboli to the periphery also occur. Several noncontrolled studies provide evidence that the risk of early recurrence is reduced to 2% to 4% with early full-dose anticoagulation. In addition, in a randomized trial a reduction was noted in recurrent emboli with the immediate anticoagulation of embolic stroke.[74] In that study, patients with suspected embolic stroke underwent CT scanning; 2 patients with hemorrhagic infarcts were excluded, and the remaining 45 patients were randomly assigned to receive either heparin immediately or no heparin. There were no recurrent emboli and no deaths among patients who received heparin immediately but two recurrent emboli and two deaths among patients not receiving heparin.

Overall, the estimated risk of symptomatic brain hemorrhage associated with immediate anticoagulation in patients with aseptic embolic stroke is 2% to 5%.[1] The current recommendations in patients with suspected aseptic embolic stroke are to do a CT scan at 24 hours or later. If there is no evidence of hemorrhage, patients should be anticoagulated with heparin followed by high-intensity warfarin therapy (INR of 3.0 to 4.5); in patients with either large embolic strokes or severe hypertension, anticoagulation should be postponed for several days because of an increased risk of late hemorrhagic transformation. In patients who have hemorrhagic transformation noted on an early CT scan, anticoagulation therapy should not be started until eight to ten days after the event.[1] If there are no recurrences after a year, the warfarin dose should be decreased to a low intensity (INR of 2.0 to 3.0).[1]

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